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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,884	11/02/2001	Cy A. Stein	0575/63293/JPW/BJA	5706

7590 04/21/2004

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/002,884	STEIN ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *11-21, 23 and 33* is/are withdrawn from consideration.

5)☒ Claim(s) *1-9,32 and 38* is/are allowed.

6)☒ Claim(s) *10,22,24-31,34-37 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the paper filed January 7, 2004 is acknowledged. The traversal is on the ground(s) the claims of Groups I-IV are not independent. Applicants point out that under M.P.E.P. § 802.1, "independent" means the groups are unconnected in design, operation, and effect, and assert that the claims of Group I-IV are related in that they are drawn to similar compounds, compositions, and methods of use relating to peptide delivery of antisense to cells. Applicants assert that two or more independent and distinct inventions have not been claimed in the subject application because the groups are not independent under M.P.E.P. § 802.01, and that restriction is thus improper under U.S.C. § 121.

However, this is not considered convincing because applicants claims are drawn to different compounds comprising a complex of an oligonucleotide with a protein, each identified by sequence. As explained previously, each complex is considered to be unrelated to the other complexes, since each complex claimed is structurally and functionally independent and distinct. This view is maintained because each complex has a combination of nucleotide sequences and protein sequences that is unique, and not shared with any other complex.

Applicants also point out that under M.P.E.P. § 803, the Examiner must examine the application on the merits even though it includes claims to distinct inventions, provided that there would not be a serious burden on the examiner if restriction were not required. Applicants assert that a search of prior art with regard any of Groups I-IV in the

subject application would necessarily identify art for other groups, as the transporting peptide component is the same in Groups I and II and in Groups III and IV.

This is not found persuasive because each group has two distinct sequences. While one of the two claimed sequences per group are shared by one other group, no group has the same two sequences. Since each sequence requires its own search, a search for both sequences would not be applicable to any other group, because no other group contains those same two sequences. A search for any of the other groups would require more than the two searches run for the elected group. Thus, the searches are not convergent, and restriction is therefore required.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-21, 23, and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed January 7, 2004.

This application contains claims 11-21, 23, and 33, drawn to an invention nonelected with traverse in the paper filed January 7, 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 depends on "[T]he method of claim 6 or 16" wherein the sequence of the oligo is SEQ ID NO: 5. However, claim 6 is a composition, rendering the claim indefinite. Substituting the term "composition" for "method" in claims 6 and 16 would be remedial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 10, 24-31, 34-37, and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of delivering the oligo of SEQ ID NO: 5 conjugated to the peptide of SEQ ID NO: 2 *in vitro* and *in vivo*, does not reasonably provide enablement for inhibition of any oligonucleotide conjugated to the peptide of SEQ ID NO: 5 the *in vivo* whole animal, or for treatment of cancerous cells in the *in vivo* whole animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The invention of the above claims is drawn to pharmaceutical compounds with a concomitantly implied pharmaceutical benefit (claim 31), comprising the conjugate of the peptide of SEQ ID NO: 2 with the oligonucleotide of SEQ ID NO: 5. The claims are also

drawn to methods of inhibition of any transcript using any oligonucleotide conjugated to the peptide of SEQ ID NO: 2, and to methods of treating cancer cells or increasing the sensitivity of cancer cells using the claimed conjugates to inhibit the expression of a protein, wherein the language of all such claims encompasses both *in vivo* and *in vitro* activity.

The specification has exemplified the *in vitro* use of 2 protein/antisense conjugates, each conjugate comprising one protein of either SEQ ID NOS: 1 or 2, and a well characterized antisense sequence of SEQ ID NOS: 5 or 6. The specification also provides broad prophetic guidance comprising treatment regimens that apply to the administration of virtually any compound to any whole animal. Such prophetic guidance, because of the extremely broad ranges and considerations, is not considered to be specific for the claimed compounds, but rather is comprised of generic guidance that may apply to the treatment of any animal with any disease.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the disclosed conjugates as pharmaceutical compounds, or for using said conjugates in any *in vivo* environment, including treating cancer cells *in vivo*. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense/protein conjugate *in vivo* based solely on its performance *in vitro* is unpredictable. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition *in vivo* is highly

unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

As indicated, the breadth of the claims embraces inhibition of gene expression or cancer treatment in the *in vivo* whole animal. However, the prior art appears to be silent as such gene inhibition using any claimed conjugate comprising an antisense oligonucleotide and a protein carrier *in vivo*, since no reference teaching any use of any similar conjugate *in vivo* has been found by the examiner. In the absence of such teachings from the prior art, one of skill in the art would be forced to rely upon the teachings of the specification to use the claimed compounds and methods *in vivo*, particularly since one of skill would understand that the use of antisense oligonucleotides or their conjugates for *in vivo* inhibition or treatment of disease is unpredictable.

In an attempt to review the prior art for the purpose of determining enablement, and because the art is apparently silent as to the *in vivo* use of protein/antisense oligo conjugates, the closest related prior art is considered to be that describing the use of antisense oligonucleotides as potential therapeutics. A discussion of the state of this art follows (i.e. antisense-mediated gene inhibition), where it is maintained that that such antisense oligonucleotides have, as a class, yet to realize significant clinical value due to

the unresolved problems in the art outlined below. To be clear, although the cited prior art does not specifically discuss oligo/protein conjugates, it is nevertheless considered to be related because the instant compounds comprise a short amino acid sequence (designed to help traverse the cell membrane barrier and guide the protein once in the cell), which is linked to an oligonucleotide, said oligonucleotide being responsible for the claimed inhibition of protein expression. For reasons given below, the state of the prior art of *in vivo* antisense-mediated gene inhibition is not considered to be predictable.

A recent (2002) review article by Braasch et al. concludes that major obstacles persist in the art of using antisense oligos in methods of using antisense *in vivo*: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to

difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target, and that "[a]ttempts to describe the *in vivo* structure of RNA, in contrast to DNA, have been fraught with difficulty." (Page 3161, second column).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states that "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379). Gewirtz adds that [t]he other major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their target . Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient."

Branch et al. discuss the problems pertaining to non-specific oligo interactions that lead to artifactual phenotypes during *in vivo* antisense administration: "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, regarding the therapeutic benefit of antisense technology in general, Branch states that "in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit (Page 46, second column).

Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent

predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Finally, Branch states that "[i]t is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo*. With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells."

Thus, it is maintained that the prior art at the time of applicants' filing would not enable the use of *in vitro* protein/antisense oligo conjugate screening techniques to support claims embracing the *in vivo* inhibition using such conjugates, let alone to claims directed to their therapeutic use *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of two *in vitro* examples coupled with broad prophetic treatment regimens enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments to *in vivo* methods of inhibition, or the *in vivo* treatment of disease as exemplified in the references above.

This is particularly true in view of the claimed breadth of the above-cited claims that pertain to treating or preventing any cancer cell suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the antisense administered, and specifically regarding the instant compositions and methods claimed.

Since the specification fails to provide any real guidance for the methods of using antisense *in vivo* or in the successful treatment or sensitization of cells to such a broad range of cancer, and since resolution of the various complications in regards to targeting a particular gene in the *in vivo* whole animal is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those sequences that are successfully delivered to target sites in appropriate cells and /or tissues such that inhibition and/or treatment is attained. In the absence of any real guidance from the specification, the amount of experimentation required to practice this would be undue, and one would have been unable to practice the invention over the scope claimed.

4. Claims 10, 24-31, 34-37, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention is as discussed above.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of

filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof.

In this case, applicants claim language is broadly drawn to methods of gene inhibition using any oligonucleotide conjugate in cells encompassing *in vivo* applications, and further to their therapeutic use, particularly in cancer. The genus of conjugates retaining these functions is not immediately envisioned because A) the genus of any antisense/SEQ ID NO: 2 conjugate is large, as evidenced by the large number of mRNA transcripts thought to be involved in cancer, and B) the genus is unpredictable, because the use of antisense compounds *in vivo* is not considered to be reliable as outlined above. Applicants have disclosed the *in vitro* inhibition of two mRNA transcripts using two well-characterized antisense RNA oligos conjugated to the subject carrier proteins. This is not considered to provide support for possession of methods drawn to using the genus of <u>any</u> antisense conjugate comprising SEQ ID NO: 2 in any method of use *in vivo*, and in particular for their use in cancer treatment, because one could not immediately envision the genus of structures of such conjugates that have the embraced function of gene inhibition *in vivo* or treatment of cancer from the disclosure of the *in vitro* inhibition of two mRNA transcripts using two well-characterized antisense RNA oligos,

particularly in view of the unpredictability of *in vivo* methods of antisense-mediated inhibition *in vivo*.

Applicants simply have not provided a representative sample of antisense/SEQ ID NO: 2 conjugates that possess the function of *in vivo* inhibition or treatment, as embraced by the claims, and one of skill could not be apprised as to which conjugates would actually possess the function of inhibition or treatment in *in vivo* methods of use. Two conjugates exemplified *in vitro* is not considered to provide adequate support for methods of using a genus of any antisense conjugated to SEQ ID NO: 2 for use in *in vivo* methods of inhibition or treatment, because this genus is both large and unpredictable, and are thus not considered to be in possession of the methods as broadly claimed.

Allowable Subject Matter

5. Claims 1-9, 32 and 38 are allowed, because the art does not teach or fairly suggest compositions comprising SEQ ID NO: 2 and methods of making same, or methods of delivering an oligonucleotide into a cell with the instantly claimed conjugates using a lysosomotropic agent.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James Douglas Schultz, PhD